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Re-evaluation Decision RVD2014-02

Amitrole

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Re-evaluation Decision

After a re-evaluation of the herbicide amitrole, Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act*, is granting continued registration for the sale and use of amitrole on spruce bareroot nursery stock (seedbeds) in Canada. An evaluation of available scientific information found that the use of amitrole on spruce bareroot nursery stock (seedbeds) has value and does not present an unacceptable risk to human health or the environment when used according to the revised label statements.

All uses of amitrole, except use in spruce bareroot seedbeds, will be phased out because human health risks of concern have been identified. These uses include control of annual and perennial broadleaf and grassy weeds in crop and non-crop sites.

The PMRA's pesticide re-evaluation program considers potential risks as well as the value of pesticide products to ensure they meet modern standards established to protect human health and the environment. Regulatory Directive DIR2001-03, *PMRA Re-evaluation Program*, presents the details of the re-evaluation activities and program structure. Re-evaluation draws on data from registrants, published scientific reports, information from other regulatory agencies and any other relevant information available.

The regulatory approach regarding the re-evaluation of amitrole was first proposed in the consultation document[1] Proposed Re-evaluation Decision PRVD2012-01, *Amitrole*. This Re-evaluation Decision Document[2] describes the decision-making stage of the PMRA's regulatory process concerning the re-evaluation of amitrole and summarizes the Agency's decision, the reasons for it and, in Appendix I, a summary of comments received during the consultation process and the PMRA's response to these comments. This decision is consistent with the proposed re-evaluation decision stated in PRVD2012-01. To comply with this decision, registrants of amitrole products will be informed of the specific requirements affecting their product registration(s) and of the regulatory options available to them.

For more details on the information presented in this Re-evaluation Decision, please refer to the related PRVD2012-01.

[1] "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

[2] "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

What Does Health Canada Consider When Making a Re-evaluation Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable if there is reasonable certainty that no harm to human health, future generations or the environment will result from use of, or exposure to, the product under its conditions or proposed conditions of registration.[3] The Act also requires that products have value[4] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

To reach its decisions, the PMRA applies hazard and risk-assessment methods as well as policies that are rigorous and modern. These methods consider the unique characteristics of sensitive subpopulations in both humans (for example, children) and organisms in the environment (for example, those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties present when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticides and Pest Management portion of Health Canada's website at healthcanada.gc.ca/pmra.

What is Amitrole?

Amitrole is a non-selective systemic Group 11 herbicide. It is registered for the control of a broad spectrum of annual and perennial broadleaf and grassy weeds on both crop and non-crop sites. Amitrole is generally applied as a broadcast spray or spot treatment (once or twice per season) using ground equipment prior to crop planting and when weeds have emerged and are actively growing. Application rates vary by use site: 0.4-0.7 kg a.i./ha on spruce seedlings, 1-4 kg a.i./ha on food/feed crops, and 1-11 kg a.i./ha on pasture, poplar and non-crop land.

Two products are currently registered in Canada under the authority of the *Pest Control Products Act* including one technical grade active ingredient and one commercial class end-use product. The registrants of the domestic class end-use products containing amitrole voluntarily discontinued their products at the time of initiation of re-evaluation; therefore, these products were not included in the re-evaluation.

Uses of amitrole belong to the following use-site categories: terrestrial food crops, terrestrial feed crops, industrial oilseed and fibre crops, forest and woodlands, and industrial vegetation control for non-food sites.

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[3] "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act*.

[4] "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (a) efficacy; (b) effect on host organisms in connection with which it is intended to be used; and (c) health, safety and environmental benefits and social and economic impact."

Health Considerations

Can Approved Uses of Amitrole Affect Human Health?

Risks of concern were identified for both dietary (food and drinking water) and occupational exposure to amitrole.

Potential exposure to amitrole may occur through diet (food and drinking water), when applying the product or by entering treated sites. When assessing health risks, two key factors are considered: the levels at which no health effects occur in animal testing and the levels to which people may be exposed. The dose levels used to assess risks are established to protect the most sensitive human population (for example, children and nursing mothers). Only those uses where exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

Amitrole was of low acute oral and dermal toxicity in laboratory animals. It was considered to be of moderate inhalation toxicity. Amitrole was minimally irritating to the eyes and non-irritating to the skin. Exposure to amitrole can cause skin sensitization.

The target organ was the thyroid gland when animals were exposed via the oral and inhalation routes. A cancer concern exists for amitrole based on increased incidences of liver tumours in mice, and thyroid and pituitary tumours in rats. Amitrole does not present a mutagenic concern.

When amitrole was administered to pregnant rabbits, an increase in the incidence of cranial malformations was observed. Due to the nature of these endpoints and their potential implications on the health of the fetus, additional protective factors were applied during the risk assessment to further reduce the allowable level of human exposure to amitrole.

Residues in Water and Food

Dietary risks from food and water are of concern.

Reference doses define levels to which an individual can be exposed over a single day (acute) or lifetime (chronic) and expect no adverse health effects. Generally, dietary exposure from food and drinking water is acceptable if it is less than 100% of the acute reference dose or chronic reference dose (acceptable daily intake). An acceptable daily intake is an estimate of the level of daily exposure to a pesticide residue that, over a lifetime, is expected to have no significant harmful effects.

Human exposure to amitrole was estimated from residues in treated crops and drinking water, and considered exposure to the general population as well as various subpopulations including the most sensitive subpopulation (infants less than 1 year of age). This aggregate (food and drinking water) exposure to amitrole represents approximately 640% of the acute reference dose for females 13-49 years of age and 2900% of the chronic reference dose for the most affected population of infants (less than 1 year of age); therefore it is of concern. The cancer risk for

amitrole was 3×10^{-3} for the general population and is also of concern. A lifetime cancer risk that is at or below 1×10^{-6} (1 in a million) usually does not indicate a risk concern for the general population when exposure occurs through pesticide residues in/on food and drinking water, and to otherwise unintentionally exposed persons. Further information on how the potential cancer risks from pesticides are assessed can be found in PMRA's Science Policy Note SPN2000-01, *A Decision Framework for Risk Assessment and Risk Management in the Pest Management Regulatory Agency*. Based on the human health concerns identified, food uses of amitrole are to be phased out.

The *Food and Drugs Act* prohibits the sale of adulterated food; that is, food containing a pesticide residue that exceeds the established Maximum Residue Limit (MRL). Pesticide MRLs are established for *Food and Drugs Act* purposes through the evaluation of scientific data under the *Pest Control Products Act*. Each MRL value defines the maximum concentration in parts per million (ppm) of a pesticide allowed in/on certain foods. Food containing a pesticide residue that does not exceed the established MRL does not pose a health risk concern.

Canadian MRLs for amitrole are currently established for wheat, barley, canola (rapeseed) and peas at 0.01 ppm. Residues in all other agricultural commodities, including those approved for treatment in Canada but without a specific MRL, are regulated under subsection B.15.002(1) of the Food and Drug Regulations, which requires that residues not exceed 0.1 ppm. However, changes to this general MRL may be implemented in the future, as indicated in Discussion Document DIS2006-01, *Revocation of 0.1 ppm as a General Maximum Residue Limit for Food Pesticide Residues* [Regulation B.15.002(1)].

Since MRLs represent the maximum concentration of pesticide allowed in/on relevant foods, accompanying the removal of food uses in Canada, the PMRA routinely revokes existing Canadian MRLs specified under the *Pest Control Products Act*. As a result, residue in such commodities is then regulated under subsection B.15.002(1) of the Food and Drugs Regulations, which requires that residues not exceed the general MRL (general MRL) of 0.1 ppm.

In the case of amitrole, as the revocation of the established MRL of 0.01 ppm for wheat, barley, canola and peas would result in residues being regulated by the higher general MRL of 0.1 ppm, the specified Canadian existing MRL of 0.01 ppm will be maintained. Details regarding the dietary risk assessment can be found in the Science Evaluation section of PRVD2012-01.

Dietary exposure to the amitrole metabolite triazolyl alanine may occur from the use of amitrole on food commodities. Residues of triazolyl alanine are regulated in Canada under the *Pest Control Products Act* not to exceed 2.0 ppm in plant commodities. This metabolite is common to triazole pesticides such as amitrole. The residue chemistry and human health risks associated with this metabolite that result from the use of all registered triazole-based pesticides will be assessed in a separate cumulative risk assessment. Additional information on triazolyl alanine can be found in PRVD2010-14, *Myclobutanil*.

Risks in Residential and Other Non-Occupational Environments

Non-occupational risks are not of concern.

No residential uses are being supported by the registrant; as such a risk assessment for this scenario was not required.

Potential exposure and risk from activities at pick-your-own facilities was considered negligible, as amitrole is not directly applied on the fruit or on the crop foliage.

Occupational Risks from Handling Amitrole

Occupational non-cancer risks to handlers are of concern for most uses of amitrole.

Most non-cancer risk estimates associated with mixing, loading, and application activities for amitrole did not reach the target Margin of Exposure (MOE) even with consideration of mitigation measures such as maximum Personal Protective Equipment (PPE) and engineering controls, and are therefore of concern. Even with maximum mitigation, the only uses that reach the target margin of exposure are spruce bareroot (seedlings and seedbeds). Using the lowest application rates for low-pressure handwand application, uses on pastures, roadsides, fencerows, and ditchbanks also reached the target MOE; however, postapplication exposure concerns for these uses were identified.

Occupational cancer risk to handlers is not of concern for most uses of amitrole.

Most occupational cancer risks are not of concern for agricultural scenarios, provided mitigation measures such as additional engineering controls, PPE and restrictions on amount handled per day are employed. Cancer risk is of concern for handlers applying to shelterbelts and poplar crops.

Occupational non-cancer risks for postapplication workers are of concern for most uses of amitrole.

Occupational postapplication risk assessments consider exposures to workers entering treated agricultural sites. Based on the current use pattern for amitrole, non-cancer risks to workers performing scouting activities in most crops did not meet current standards and are of concern. Even with mitigation measures, the Restricted-Entry Intervals (REIs) required to mitigate postapplication risk range from four to 70 days and may not be agronomically feasible for most crops. The only use with an agronomically feasible REI is spruce bareroot (seedbeds) with an REI of four days.

Occupational cancer risks for postapplication workers are not of concern for all uses of amitrole when REIs are considered.

Postapplication cancer risks for workers entering treated sites were not of concern, provided that the long REIs required for entry into a treated site (based on the non-cancer assessment) were considered.

Environment Considerations

What Happens When Amitrole is Introduced Into the Environment?

Amitrole poses a potential risk to terrestrial and aquatic organisms; therefore additional risk reduction measures need to be observed.

When amitrole is released into the environment, some of it can be found in soil and surface water. In soil, amitrole is broken down by microbes; thus, it is not expected to persist in the environment. Laboratory studies indicate that amitrole could leach in soil. However, field studies (relevant to Canadian conditions) conducted in the United States of America, detected amitrole and its transformation products in only the top 30 cm deep soil layer. Leaching is probably offset by microbial transformation.

Amitrole poses a risk to terrestrial and aquatic organisms. Birds and small wild mammals are at risk in and around the site of application due to the consumption of contaminated food items. These risks were determined to be of concern and cannot be mitigated.

Value Considerations

What is the Value of Amitrole?

Amitrole contributes to weed management in a variety of crop and non-crop sites.

Amitrole controls many annual and perennial broadleaf and grassy weeds. It is generally considered to be a specialty herbicide for managing particular perennial broadleaf weeds (for example, Canada thistle in minimum tillage field crop production), toxic plants (for example, poison ivy and poison oak in non-cropped areas), and specific noxious weeds (for example, cattails and horsetails in pastures, shelterbelts or non-crop lands).

As a niche product, the amount of amitrole used in Canada is limited when compared with many other herbicides. Active ingredients other than amitrole are registered for use on all sites listed on the amitrole label. However, for a few difficult to control weeds (for example, cattails, poison oak, milkweed, and hoary cress), only one alternative herbicide is registered.

Measures to Minimize Risk

Based on health concerns, the PMRA is cancelling the registration of amitrole and all associated end-use products for all uses with the exception of use on spruce bareroot nursery stock (seedbeds).

Appendix II lists all required label amendments.

What Additional Scientific Information is Being Requested?

The following data is required under section 12 of the *Pest Control Products Act* for continued registration:

Chemistry Data

- Analytical data from fiver recent batches of the technical grade active ingredient to adequately identify any impurities of concern.

Other Information

Any person may file a notice of objection[5] regarding this decision on amitrole within 60 days from the date of publication of this Re-evaluation Decision document. For more information regarding the basis for objecting (which must be based on scientific grounds), please refer to the Pesticides and Pest Management portion of Health Canada's website (Request a Reconsideration of Decision) or contact the PMRA's Pest Management Information Service.

[5] As per subsection 35(1) of the *Pest Control Products Act*.

List of Abbreviations

ATPD	Area Treated Per Day
DNA	deoxyribonucleic acid
EC	European Commission
EU	European Union
ha	hectare
IARC	International Agency for Research on Cancer
IPCS	International Programme of Chemical Safety
L	litre
MOA	Mode of Action
MOE	Margin of Exposure
MRL	Maximum Residue Limit
NAFTA	North American Free Trade Agreement
PHED	Pesticide Handlers Exposure Database
PMRA	Pest Management Regulatory Agency
PPE	Personal Protective Equipment
PRVD	Proposed Re-evaluation Decision
q_1^*	cancer potency factor
REI	Restricted-Entry Interval
RVD	Re-evaluation Decision
SPSF	Statement of Product Specification Form
T3	triiodothyronine
T4	thyroxine
TPO	thyroid peroxidase
TSH	thyroid stimulating hormone

Appendix I Comments and Responses

In response to the consultation document PRVD2012-01, *Amitrole* comments relating to the health and value assessments were received from the registrant and from one member of the public.

1.0 Comments Relating to Health

1.1 Comment – Carcinogenicity Assessment

The registrant noted that the PMRA established a unit risk (q_1*) value of 0.328 $(mg/kg\ bw/day)^{-1}$ based on thyroid follicular cell tumours in male rats.

Amitrole has been extensively reviewed by various regulatory and health authorities over its long history of use. Special attention in the toxicological dossier has been paid to the carcinogenic potential of amitrole. As new data and studies became available, a better understanding of the mechanisms involved and their significance to human health risk was obtained. The classification of amitrole as a "possible" carcinogen by various authorities has now evolved to a "not likely to be a carcinogen" decision.

Current carcinogenicity classifications by major pesticide regulatory authorities are summarized in the following table:

Agency	Decision	Reference Documents
European Union	Withdrawal from category 3 & withdrawal of risk phrase R40. (2000) Into force on 20.04.2004	**SCP/AMITR/002-Final (2000)** **ECBI/24/00 – Rev2 (2000)**
International Agency for Research on Cancer (IARC)	Withdrawal from Group 2B. Classified as Group 3 = "non classifiable as carcinogen for human" (2001)	**WHO IARC (2001)**
United States Environmental Protection Agency (USEPA)	Reclassification by "Not Likely to be Carcinogenic to Humans at Doses that do not alter Rat Thyroid Homeostasis" (2006)	**USEPA CARC (2006)**

The registrant recently assessed these various decisions in conjunction with an application to Japan to establish MRLs for amitrole in various commodities. The registrant submitted the following document with their comment:

> Vanhaecke, M. 7 July 2007. Establishment of Maximum Residue Limits (MRL) for Agrochemicals used outside Japan; Japan Food Sanitation Law Notification No. 499; Amitrole (CAS 61-82-5); Part II Toxicology - Evaluation & Classification of the Carcinogenic Potential for Amitrole. Nufarm sas.

It is the registrant's belief that the PMRA assessment may overstate the cancer risk, and asks the PMRA to consider the determinations of other regulators in a re-assessment.

Will PMRA be re-assessing the cancer risk?

PMRA Response

The PMRA review of the amitrole toxicology database identified a treatment-related increased incidence of thyroid tumours in rats. Based on a suite of in vivo and in vitro genotoxicity assays, amitrole does not damage DNA. The PMRA considered a non-genotoxic Mode of Action (MOA) in the rat involving thyroid peroxidase (TPO) inhibition that has been proposed in the scientific literature to support a Margin of Exposure (MOE) based risk assessment for this tumour response.

In the suggested Mode of Action (MOA), amitrole inhibits thyroid peroxidase, resulting in decreased serum levels of thyroxine (T4) and triiodothyronine (T3). Decreased thyroid hormone levels cause increased secretion of Thyroid Stimulating Hormone (TSH) which, if sustained, leads to thyroid hypertrophy, hyperplasia and neoplasia. This general MOA has been well characterized in the literature and is biologically plausible in rats.

In 2001 evaluations of amitrole, the International Agency for Research on Cancer and the European Commission (EC) accepted this mode of action and, therefore, did not conduct quantitative cancer risk assessments (PMRA #1829150, 1748609). In 2006, the USEPA reclassified amitrole to "not likely to be carcinogenic to humans at doses that do not alter rat thyroid homeostasis" (PMRA #1829148).

The PMRA's re-evaluation considered current cancer risk assessments for amitrole completed by other major pesticide regulatory authorities, including the assessments listed by the registrant. The document provided by the registrant during the comment period following publication of the proposed decision does not contain any additional information that the PMRA did not already consider during the evaluation of the MOA. Therefore, no new information was submitted by the registrant.

During the evaluation of amitrole, the PMRA did not receive a MOA assessment for amitrole from the registrant. Therefore, the PMRA used The International Programme of Chemical Safety (IPCS) framework for assessment of MOAs to analyze the available amitrole toxicological database for evidence in support of the proposed mode of action for rat thyroid tumours. It should be noted that limitations in the design of several studies (non-guideline study design; lack of measurement of all key events in each study; insufficient animals in sampled groups) hindered the evaluation of temporal relationships and dose-response relationships. The analysis is summarized below.

Key Steps in the Mode Of Action:

TPO inhibition:
The first key event in the proposed MOA is the dose-dependent inhibition of TPO. This was demonstrated in vitro using lactoperoxidase (similar in structure and function to TPO) in the presence of excess of amitrole, with increasing levels of hydrogen peroxide.

Hormone response to TPO inhibition:
Following the inhibition of TPO, the second key event in the proposed MOA is the reduction of serum T3 and T4. There was a lack of consistency observed for the thyroid hormone levels in toxicity tests using rats. The expected decreases in T3 and T4 were observed; however, unexpected increases in T3 levels were noted in treated animals in one intermittent dosing chronic rat study. Furthermore, when T3 and T4 hormone levels were measured, a clear dose-response was not noted at all examined time points, or the observed downward trend in T3 and T4 levels did not progressively decrease with increasing doses of amitrole.

Elevated TSH levels:
Following a reduction in serum T3 and T4, increased serum TSH (the third key event in the proposed MOA) was expected. However, TSH was only measured in one subchronic toxicity study and one range-finding study using rats. While increased TSH was noted in all treated groups in the range-finding study, only high dose group animals from the subchronic study showed elevated TSH. In the same subchronic study in rats, thyroid hormones were measured at three time points, but no dose response was evident for T4 or TSH levels, and a lack of consistency was observed in T3 levels in both sexes. Therefore, T3 and T4 data could not be correlated with the TSH levels. In addition, the expected consistent progressive changes of hormone levels were not noted, even though a dose response was observed in thyroid weight effects, thyroid hyperplasia and follicular cell carcinoma.

Pathological changes in the thyroid:
The fourth key event in the proposed MOA is pathological changes in the thyroid. The expected changes, (increased thyroid weight and follicular cell hyperplasia followed by tumours) were observed across the database.

The temporal relationship between the key events of the proposed MOA was also examined. No study was available in which hormone measurements and macroscopic observations were made at each of the same time points. Therefore, it was difficult to make a definite conclusion about the temporal relationship between TPO inhibition, T3, T4 and TSH changes, thyroid weight increases and thyroid follicular cell hyperplasia and/or thyroid follicular carcinoma. Thus, the proposed MOA could not be supported.

Other possible MOAs:
Although amitrole has been demonstrated to be a TPO inhibitor, other modes of action which result in the same outcome (thyroid follicular cell tumours) have not been explored. Other possible MOAs include: damage to follicular cells, inhibition of iodine uptake, inhibition of thyroid hormone release, inhibition of 5'-monoiodinase activity, and enhancement of thyroid hormone metabolism.

Conclusion:
As noted in PRVD2012-01, the proposed thyroid follicular cell tumour MOA lacked consistent hormone data, a temporal relationship for the sequence of key events could not be established, and a clear dose-response was not observed in the database. This is partially the result of limitations in many of the available toxicity studies. As a result of these gaps, the PMRA could not support the proposed MOA and has defaulted to the use of a linear quantitative cancer risk assessment model. A unit risk (q_1*) of 0.328 $(mg/kg\ bw/day)^{-1}$ was determined based on thyroid follicular cell tumours in male rats in the chronic intermittent dosing study.

Other tumours identified in the database included pituitary cell carcinoma/adenoma in rats and hepatocellular carcinoma/adenoma in mice. There is no clear consensus on the significance of these tumours among international regulatory agencies. IARC Working Group concluded that "based on the lack of genotoxicity of amitrole, was that [sic] the liver tumours in mice and benign pituitary tumours in rats were also produced by a non-genotoxic mechanism" (2001); however no mechanism was provided by the agency. The presence of pituitary tumours in rats was considered by the USEPA to be consistent with the accepted MOA for thyroid tumours, a disruption of the thyroid-pituitary hormonal homeostasis. The USEPA concluded that the increased incidence of hepatocellular carcinoma observed in the mouse was no longer of concern after re-analysis of unpublished data and due to the low confidence in published studies in which it was observed (the liver tumours were not treatment related). While the PMRA agrees with the conclusions drawn by the USEPA regarding the unpublished chronic mouse study, the agency continues to have concerns for the incidences of hepatocellular carcinoma and adenoma observed in one published study (PMRA #1839761). The feeding study included only a single dose, and therefore a q_1* could not be generated. The risk assessment based on the thyroid follicular carcinoma/adenoma in rats is considered to be protective of other noted tumours, considering the large q_1* value, and higher incidence of tumours, as compared to liver and pituitary tissues.

Therefore, PMRA will maintain its current position unless sufficient data are provided to adequately address the identified gaps in the MOA.

1.2 Comment – Amount Handled

Postharvest treatment of food or feed crop fields and alfalfa renovation would be of similar treatment area size, application technique and purpose to preplanting treatments. The registrant estimates 15% of national annual sales are used in these use scenarios. Typical use rates are 1-2 kg a.i./ha.

The remaining 5% of product use is in backpack or low-pressure handwand applications in scenarios such as application to apple orchard floors, in shelterbelts, and spot treatment of specific weed problems in non-crop areas. Individual treatment areas are small with backpack and low-pressure handwand applications as most farm operators or labourers are not inclined to participate in many consecutive hours of manual labour. The 150 L/day value used in risk assessment calculations (for example, Appendix V of the PRVD) represents 15 fillings of a 10 Litre backpack sprayer. The registrant speculates four fills of a 10 Litre backpack sprayer is as much as most workers would tolerate before seeking a more mechanized application technique.

PMRA Response

Alfalfa renovation Area Treated Per Day (ATPD) was assumed to be 68 ha (application by farmer) and 300 ha (custom application) while postharvest treatment of food/feed crop fields were assumed to be 100 ha (application by farmer) and 400 ha (custom application). Since the crops listed under "postharvest" description included grain commodity in addition to alfalfa, the ATPD assumed was the default of the largest area, which was grain crop. Even if alfalfa was separated out to use the lower ATPD values (68 ha and 300 ha), the occupational exposure risk concerns would still remain.

The amount applied by a backpack sprayer per day (150 L/day) is a default value used by the PMRA (based on the USEPA Policy #9 – *Standard values for daily acres treated in agriculture, Science Advisory Council for Exposure*, originally published 1 April 1999, revised 5 July 2000). The amount of product applied using a backpack sprayer could be changed if verified data is provided to demonstrate an amended value. To reduce exposure to acceptable levels for non-cropland use sites using the "backpack" scenario, mixers/loaders and applicators would need to be limited to 20 L/day (agronomic feasibility of such a restriction would require prior consultation). However, the outcome of the overall risk assessment may not change as there are other risk concerns that would need to be addressed as well (for example, exposure during postapplication activities).

1.3 Comment – Exposure Estimates

The registrant had some questions related to the values used in the risk assessment calculations, and believed the answers would assist in their comprehension of the impact of the critical values used in the calculations.

In Appendix V, Table 1-A and Table 1-B (Occupational Exposure and Non-Cancer Risk Assessments, High and Low rates, respectively), the calculated daily exposure (dermal and inhalation) is expressed as mg/kg/day. The footnotes to these tables describe the formulas to calculate these values, expressed as µg/kg/day.

We are unable to duplicate the calculation of daily exposure values without additional information on the specific unit exposure values and adjustment factors for personal protective equipment used in the PMRA calculations. The registrant would appreciate receiving more detailed information on the specific values used in the calculations.

PMRA Response

The specific unit exposure values used for the MOE calculations were taken mainly from the Pesticides Handlers Exposure Database (PHED). Spruce bareroot scenarios used unit exposure values from a previously submitted exposure study (PMRA #1741794) and not PHED. A sample calculation is provided below:

Sample Calculation for Soybeans:

Amount handled per day = application rate × ATPD/CF
= 4000 g a.i./ha × 100 ha/day / (1000 g/kg) = 400 kg a.i.

Where:

- Amount handled per day = kg a.i.
- Application rate = as determined from labels (g a.i./ha)
- ATPD = Area treated per day (ha/day)
- CF = conversion factor of 1000 to convert grams to kilograms

Dermal exposure = Amount handled per day × dermal unit exposure × DA / (bw × CF)
= 400 kg a.i. × 84.12 µg/kg/day × 20% / (70 kg × 1000 µg/mg)
= 0.096137 mg/kg/day

Where:

- Dermal exposure = mg/kg/day
- Amount handled per day = kg a.i.
- Dermal unit exposure = from PHED tables (µg/kg/day)
  = (51.14 for open mixing/loading of liquids + 32.98 for open cab groundboom application)
- DA = dermal absorption, assumed 20%
- CF = conversion factor of 1000 to convert µg/kg/day to mg/kg/day

Inhalation exposure = Amount handled per day × inhalation unit exposure / (bw × CF)
= 400 kg a.i. × 2.56 µg/kg/day / (70 kg × 1000 µg/mg)
= 0.014629 mg/kg/day

Where:

- Inhalation exposure = mg/kg/day
- Amount handled per day = kg a.i.
- Inhalation unit exposure = from PHED tables (µg/kg/day)
  = (1.6 for open mixing/loading of liquids + 0.96 for open cab groundboom application)
- CF = conversion factor of 1000 to convert µg/kg/day to mg/kg/day

The adjustment factors for Personal Protective Equipment (PPE) are as follows: a reduction of exposure to covered body parts (arms, chest, back, thighs, lower legs) by a factor of 75% for coveralls over a single layer of clothing, 90% for chemical-resistant coveralls over a single layer of clothing.

In reference to Appendix V of the PRVD, though the daily exposure is expressed as mg/kg/day in the table and the footnotes describe the values as µg/kg/day, a conversion factor of 1000 was used within the calculation as demonstrated above in the sample calculation.

1.4 Comment – Dermal Absorption Factor

The registrant commented on the dermal absorption factor of 20% used by PMRA in the calculation of daily exposure, and the observation from section 3.2.1.4 of the PRVD that this estimate could be refined. The registrant noted that lower values of 1% and 0.5% have been used by the European Commission (2001) and the USEPA (1996), respectively.

The registrant referenced three dermal absorption studies, two of which were relied upon in the PMRA evaluation. These were an in vivo animal study (Puhl, 1985; PMRA #1170819), an in vitro animal and human study (Gelis, 2007; PMRA #1741795), and an in vitro human study (Marty, 1999).

It was suggested that PMRA could apply the European Union (EU) approach as articulated in its guidance document on dermal absorption (SANCO/222/2000 rev 7) to revise the dermal absorption estimates. That is, to apply the ratio of the in vitro human and animal absorption values to scale the results of the animal in vivo study to determine an estimate for in vivo human skin.

Based on the European Union evaluation paradigm, the registrant proposed a dermal absorption value of 0.5%, and noted that this is comparable to the factor used by other agencies to estimate the risk to operators and workers.

PMRA Response

Currently, in vitro studies are not accepted alone, but can be accepted as part of a triple pack approach with in vivo data in order to refine the estimation of dermal absorption. As outlined in the 2008 North American Free Trade Agreement position paper on the use of in vitro dermal absorption data in risk assessment, when in vitro data are being submitted, it is recommended that they be submitted as part of a triple pack of in vitro human and animal studies and an in vivo animal study. Under this triple pack approach, if an in vitro technique performed using animal skin is shown to be a good predictor of animal in vivo dermal absorption for a particular compound, then the same technique conducted in vitro with human skin may be useful in extrapolating to humans. In other words, when laboratory studies demonstrate that the ratio of the animal in vitro to in vivo dermal absorption factor is close to one, a human in vitro study conducted under the same conditions as the animal test is likely to be a good predictor of human dermal absorption. This approach differs from that of the EU, as the ratio of the human and animal in vitro studies is not used to directly scale the dermal absorption factor. The usefulness of the data would necessarily be dependent on the validity and applicability of the experimental design and the quality and integrity of the data. Consideration of the 'minimal standards' discussed in the position paper (such as same dose/duration regime), would also be required prior to use of the triple pack approach for amitrole.

The submitted in vitro study (PMRA #1741795) and in vivo study (PMRA #1170819) were considered in the context of a triple pack approach. However, the studies did not meet the minimum standards because the rat species, doses, durations (exposure and study length), area dosed and dose vehicles differed between the available studies. Overall, there is more confidence in the in vivo study to be predictive of dermal absorption. As the submitted studies did not meet

the minimum criteria for the triple pack approach, a weight-of-evidence approach based on the in vivo study was used to estimate the 20% value. Based on the criteria used by PMRA, this dermal absorption value was not overestimated. Skin-bound residues were included in this estimate as the fate of these residues was not characterized beyond the 10 hour time point.

The PMRA has not received the referenced study (Marty, J.P. 1999. In vitro Dermal Absorption of 14C Amitrole on Human Skin. Pharmacy University). As noted above, the rat and human in vitro study (PMRA #1741795) did not meet the minimum standards for use in a triple-pack approach. In the absence of a complete set of triple pack studies that meet the minimum requirements, PMRA will continue to rely on the available in vivo study to estimate dermal absorption. While potentially informative, the additional information from the human skin in vitro study is unlikely to impact the determination of dermal absorption or the overall risk assessment as there are other risk concerns that need to be addressed as well (for example, dietary and aggregate risks).

1.5 Comment – Residue and Maximum Residue Limits

PMRA is proposing that all MRLs for amitrole in Canada be revoked. If the decision to discontinue most uses stands as proposed, MRLs for some imported commodities such as European olives and grapes will need to be established.

Analytical methods measuring amitrole, triazolylalanine and aminotriazolylalanine in grapes and olives have been developed and validated.

> Gemrot, F. 2011. Amitrole – Validation of Analytical Method for amitrole, triazolylalanine and amiinotriazolylalanine in Grapes. Eurofins\ADME Bioanalysis Study S10-03263.
>
> Gemrot, F. 2011. Amitrole – Validation of Analytical Method for amitrole, triazolylalanine and amiinotriazolylalanine in Olives. Eurofins\ADME Bioanalysis Study S10-03184.

Residue trials measuring amitrole, triazolylalanine and aminotriazolylalanine were conducted on grapes and olives. No residues above the Limit of Detection (LOD) were found.

> Amic, S. 2012. Amitrole – Residue Study in Grapes in France in 2011. Eurofins\ADME Bioanalysis Study S11-01150.
>
> Amic, S. 2011. Amitrole – Residue Study in Olives in Spain in 2010. Eurofins\ADME Bioanalysis Study S10-03088.
>
> Amic, S. 2011. Amitrole – Residue Exploratory Trial in Processing Olives in Spain in 2010. Eurofins\ADME Bioanalysis Study S10-03541N.

A stability study of amitrole, triazolylalanine and aminotriazolylalanine in grapes and olives was conducted.

> Amic, S. 2011. Determination of Storage Stability of Amitrole in Grapes and Olives under Freezer Storage Conditions. Eurofins\ADME Bioanalysis Study S10-03264.

PMRA Response

In order to establish MRLs for imported commodities such as European olives and grapes, the PMRA requires a complete and robust residue chemistry database (for example, metabolism studies, analytical methodology, freezer storage stability, supervised residue trials). Any request for new or revised MRLs should be made through the PMRA submission process.

1.6 Comment – Dietary Exposure

How does dietary exposure to amitrole occur in cropland uses when amitrole is not applied directly to crops other than in spot treatment situations? Otherwise amitrole is applied either prior to seeding or following crop harvest or in summer fallow.

PMRA Response

Following a preplanting and/or postharvesting treatment, there is a potential for the uptake of amitrole residues from soil by the crops grown in the treated fields. In addition, amitrole residues can get into drinking water sources. Therefore, dietary exposure may occur as a result of ingestion of amitrole residues in the daily diet (food and drinking water).

2.0 Comments Relating to Value

2.1 Comment – Value Considerations and Use Estimates

As a niche product, amitrole is not widely or intensively used and its usage can be categorized into three aspects:

(1) Major use (about 80%): mainly used as a preplanting treatment for control of dandelion and other weeds in soybean and corn in Ontario or for control of volunteer glyphosate tolerant canola and dandelion in canola and peas in Alberta. Nationally, the amount of use is extremely low. The estimated treated area is about 9000 ha in each of Ontario and Alberta (based on the typical rate of 1 kg a.i./ha). The estimated percent crop treated is less than 1% for each of the above-listed crops. Amitrole is not used on a "whole-farm" basis but on target problem areas or fields where farmers cannot resolve the weed control needs with typical treatments, for example, glyphosate. The typical area treated by individual users is about 40 ha in Ontario and 64 to 128 ha in Alberta;

(2) Lesser use (about 15%): postharvest treatment of food or feed crops and alfalfa renovation both at a rate of 1-2 kg a.i./ha; and

(3) Minor use (about 5%): application using backpack or low pressure hand wand to apple orchards, shelterbelts and spot treatment of specific weed problems in non-crop areas.

Amitrole is of value in managing herbicide resistant weed populations including Group 2 herbicide resistant kochia and glyphosate-resistant Canada fleabane, giant ragweed and kochia. It controls volunteer glyphosate-tolerant canola. It provides an effective tool to manage dandelion which is increasingly abundant due to reduced tillage cropping practices. It is very effective for

the control of field horsetail in Western Canada since it provides systemic activity to control the subsoil portions of the plant. Many alternative herbicides that can be used to control these weeds can have negative effects on subsequently seeded sensitive crops (for example: phenoxy herbicides, sulfonylurea herbicides and others), or are in others ways inadequate to provide the level of weed control desired, or require multiple repeated applications to achieve the effectiveness offered by one application of amitrole.

Although amitrole is not widely or intensively used, to phase it out would deny its use to those crop producers who find it a valuable tool in controlling glyphosate tolerant annual weeds and perennial broadleaved weeds where there are few alternatives.

PMRA Response

The PMRA recognizes that amitrole is a niche product that has value in weed management on various crops and non-crop areas. However, risk concerns have been identified for all registered uses, except the use on spruce bareroot nursery stock. Uses that pose risk concerns are to be phased out as proposed in PRVD2012-01.

3.0 Comments Relating to the Availability of Other Studies

3.1 Comment – New Field Operator Exposure Study

A new field operator study measuring amitrole excreted in urine is available. This study is conducted on 40 subjects applying 12 L/ha of a formulation containing 229 g/L of amitrole and 215 g/L of ammonium thiocyanate by tractor drawn sprayer. Two crops were tested: grapes in France and olives in Spain.

> Thouvenin, I. 2012. Determination of External and Systemic Exposure (Using Biomonitoring in Urine) of Operators to Amitrole during Downward Application. STAPHYT Report ChR-11-8256.

A position paper justifying the use of aminotriazole as a biological marker has been developed summarizing all the kinetic data that are available.

PMRA Response

The PMRA acknowledges the availability of a new field operator exposure study in possession of the registrant; however the PMRA will not use this study to revise the current worker exposure assessment. This is based on confidence in the existing assessment, as well as consideration of risks identified beyond those for workers (for example, dietary and aggregate risks).

The occupational exposure assessment presented in the PRVD primarily used PHED data to assess the supported uses of amitrole. A chemical specific study was also assessed (PMRA #1741794) and used for scenarios where PHED may underestimate risk in the spruce bareroot use sites. Despite certain limitations (for example, low sample size for certain scenarios, inconsistencies between replicate conditions, and high coefficients of variation), the chemical specific study served to verify that PHED does not greatly over nor underestimate potential exposure to amitrole.

There is confidence that the PHED based exposure assessment is representative of the registered Canadian uses and application methods of amitrole. While the new field operator exposure study may refine the exposure estimates, it is unlikely to change the assessment to the degree where worker risks are considered acceptable. This conclusion is based on the very low margins of exposure calculated for most of the exposure scenarios, the adequacy of the worker exposure database for amitrole, and concordance of the Wilson study (PMRA #1741794) with the PHED estimates.

3.2 Comment – Analytical Profile Study

An additional study on the analytical profile of amitrole can be submitted upon request.

> Da Conceicao, L. 2012. Amitrole Technical – Analytical Profile of 5 Batches. Nufarm Study 01463. (Analysis of hydrazine content is in progress.)

PMRA Response

The following chemistry data listed in PRVD2012-01 is a requirement for continued registration:

DACO 2.13.4	Impurities of human health or environmental concern. In the manufacture of amitrole, one of the starting materials is hydrazine, used in 60% excess. The chemistry data do not indicate whether or not the technical product was analyzed for hydrazine as an impurity. Hydrazine is an impurity of concern as identified in Section 2.13.4 of Dir98-04, *Chemistry Requirements for the Registration of a Technical Grade of Active Ingredient or an Integrated System Product*. Analytical data from five recent batches of the technical grade active ingredient to 0.1% as per Section 2.13.3 of Dir98-04 will be required. If it is found at any level, it must be added to the Statement of Product Specification Form with the appropriate nominal level and upper limit.

Therefore the available study on the analytical profile of amitrole is required for continued registration.

3.3 Comment - Residues in Arthropods Study

Additional studies on the residues of amitrole in arthropods are available and can be submitted upon request.

> Knäbe, S. Residues of Amitrole in Arthropods as Food Sources for Wild Birds and Mammals after Application of Weedazol (Northern Germany 2008) – Final Report. Feb 18, 2009. Study S09-00383. Eurofins-GAB GmbH.
>
> Mende, P. Residues of Amitrole in Arthropods as Food Sources for Wild Birds and Mammals after Application of Weedazol (Northern Germany 2008) – Analytical Phase Report. Feb 18, 2009. Study S09-00383. Eurofins-GAB GmbH.

PMRA Response

There are no outstanding environmental toxicity data requirements.

Appendix II Label Amendments for Commercial Class Products Containing Amitrole

The following label amendments are required for technical, manufacturing, and end-use products as applicable.

I. As a result of the re-evaluation of amitrole, the following label amendments are required for Reg. No. 25684:

> **All uses except for the use on spruce bareroot nursery stock should be removed from the product label.**

II. Uses Requiring Mitigation

- All uses of amitrole must be removed from the label.
- Mitigation measures are required in order to reduce the risk of occupational exposure, thus the "special use applications" of the label should be amended to reflect the remaining registered amitrole use: spruce bareroot nursery stock (seedbed).
- The following use is to be phased out on the "special use applications": spruce bareroot (seedlings).

III. Use Precautions

In the "special use applications," the text in the "Directions for Use" must be adjusted to reflect the remaining use on spruce bareroot (seedbeds) and to remove the statements about spruce bareroot (seedlings) and transplanting:

> *To be applied only on Spruce (not Pine, Tamarack or other evergreen species). Application can be made in the first year in seedbeds, but only after the seedlings have set bud, at a rate of 1.7 L/ha.*

Add the following statements to all amitrole products:

> *Potential skin sensitizer.*
>
> *Not for use by homeowners or other uncertified users.*
>
> *Do not use in residential areas. Residential areas are defined as sites where bystanders including children may be potentially exposed during or after spraying. This includes around homes, school, parks, playgrounds, playing fields, public buildings or any other areas where the general public including children could be exposed.*

Add to DIRECTIONS FOR USE:

Field sprayer application: **DO NOT** apply during periods of dead calm. Avoid application of this product when winds are gusty. **DO NOT** apply with spray droplets smaller than the American Society of Agricultural Engineers (ASAE) medium classification. Boom height must be 60 cm or less above the crop or ground.

DO NOT apply by air.

Buffer zones:

For tank mixes, consult the labels of the tank-mix partners and observe the largest (most restrictive) buffer zone of the products involved in the tank mixture and apply using the coarsest spray (ASAE) category indicated on the labels for those tank mix partners.

IV. Postapplication Label Statements – Restricted Entry Intervals (REI)

Labels must be amended to reflect the REIs that reduce the risk for postapplication workers:

Spruce bareroot (seedbeds):	*A REI of 4 days after application is required to perform postapplication activities in treated areas.*

V. Add to GENERAL INFORMATION:

"Do not apply more than twice per year."

VI. Add to ENVIRONMENTAL HAZARDS:

TOXIC to terrestrial plants, birds, mammals and aquatic organisms.

References

A. Studies/Information Provided by the Applicant/Registrant - Unpublished

Studies Considered in the Health Assessment – Occupational Exposure

PMRA Document Number	Reference
1170819	Final Report - Dermal Absorption Of 14C- Amitrole In Male Rats (6158-105;7.2.1.1;ref 48), DACO: 5.8,6.4
1741795	2007, Comparison Of The In-vitro Percutaneous Absorption Of Weedazol Tl Old (CA0123) Versus New (CA2210) Generation, DACO: 5.8
1741794	2002, Amitrole -Ammonium Thiocyanate Pesticide Exposure Study To Mixers/Loaders And Applicators During Typical Applications Of Weedazol Tl In France In 1999, DACO: 5.5

B. Additional Information Considered – Published

Studies Considered in the Health Assessment – Toxicology

PMRA Document Number	Reference
1829148	Cancer Assessment Review Committee, CARC, United States Environmental Protection Agency. (2006) Evaluation of the carcinogenic potential of amitrole (fifth review). PC Code 004401
1748609	European Commission. (2001) Review report for the active substance amitrole
1829150	IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 79. (2001) Some Thyrotropic Agents. 381-410
1839761	Vesselinovitch SD. 1983, Perinatal Hepatocarcinogenesis - Biological Research In Pregnancy And Perinatology, Volume 4, Number 1, Pages 22-25, DACO: 4.8